The association between heavy metals, endometriosis and uterine myomas among premenopausal women: National Health and Nutrition Examination Survey 1999–2002

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BACKGROUND: It has been hypothesized that exposure to exogenous estrogens may be associated with endometriosis and uterine myomas. We sought to investigate the association between heavy metals which have been shown to be hormonally active and these disorders using data from the National Health and Nutrition Examination Survey, 1999–2002. METHODS: Women aged 20–49 years who had data on metals and the outcomes of interest, were premenopausal and neither pregnant nor breastfeeding were eligible (n = 1425). Lead, cadmium and mercury were measured in whole blood. Diagnosis of outcomes was based upon self-report. Logistic regression was used to examine the association between tertiles of heavy metals and disease adjusting for age, race/ethnicity, use of birth control pills prior to diagnosis and smoking status at diagnosis. RESULTS: A dose–response association between cadmium and endometriosis was observed [tertile 2 versus 1: adjusted odds ratio (OR) = 1.94, 95% confidence interval (CI): 0.73–5.18; tertile 3 versus 1: adjusted OR = 3.39, 95% CI 1.37–8.40]. This association persisted in subanalyses: (i) limiting analysis to women diagnosed in the past 10 years and (ii) limiting analysis to women diagnosed since last pregnancy, although limited by sample size. CONCLUSIONS: These results must be interpreted with caution given the cross-sectional study design. The observed association between cadmium and endometriosis deserves further investigation in properly designed studies.

Keywords: lead; cadmium; mercury; endometriosis; leiomyoma

Introduction

Endometriosis and uterine myomas are prevalent gynecological disorders. Approximately 10% of women of reproductive age in the USA are diagnosed with endometriosis (Wheeler, 1989) with lesions present in 20–50% of women undergoing laparoscopy for infertility (Matorras et al., 1995). The incidence of uterine myomas is 2–13 cases per 1000 person-years with a lifetime cumulative incidence of 70–80% (Schwartz et al., 2000; Baird et al., 2003). Given the prevalence of disease and cost of treating the associated problems of infertility, pelvic pain and abnormal uterine bleeding, endometriosis and uterine myomas represent a major public health problem in the USA (Mauskopf et al., 2005; Gao et al., 2006a,b). Despite this, few risk factors have been identified for either of these disorders.

Endometriosis has been associated with being of white race, higher socio-economic status, leaner body mass, earlier age at menarche, non-smoker, exercise and various environmental exposures (Mayani et al., 1997; Eskenazi et al., 2002; Missmer and Cramer, 2003; Hemmings et al., 2004; Hediger et al., 2005; Louis et al., 2005). Myomas have been associated with being of black race, an increased body mass index (BMI) and non-smoker (Schwartz et al., 2000). Both uterine myomas and endometriosis are considered estrogen-dependent diseases and have been associated with increased expression of estrogen receptor-α (ERα) in diseased tissues compared with non-diseased tissues (Brandon et al., 1995; Benassayag et al., 1999; Matsuzaki et al., 2001; Wang et al., 2001). Given both diseases are hormonally related, it has been hypothesized that exposure to exogenous estrogens may be associated with disease development (Hunter et al., 2000; Schwartz et al., 2000; Birnbaum and Cummings, 2002; Rier, 2002).

Some heavy metals have been shown to have endocrine disrupting properties, interfering with the hypothalamic–pituitary–ovarian (HPO) axis. Many adverse reproductive effects related to heavy metals have been observed in both toxicological and epidemiological studies; however, studies in relation to endometriosis and uterine myomas have been limited and inconsistent (Gerhard et al., 1998; Krugner-Higby et al., 2003; Heilier et al., 2004; Nasiadek et al., 2005; Heilier et al., 2005).
et al., 2006). Lead, cadmium and mercury have all been shown to inhibit the binding of estradiol to the ERα receptor (Stoica et al., 2000; Martin et al., 2003; Brama et al., 2007) with lead and mercury having potential anti-estrogenic effects (Young et al., 1977; Martin et al., 2003) and cadmium having estrogenic effects (Young et al., 1977; Stoica et al., 2000; Johnson et al., 2003; Brama et al., 2007). All three metals are ubiquitous in the environment; however, the main sources of lead exposure are through lead-based paint, and contaminated soil, dust and drinking water; cadmium exposure is primarily through cigarette smoke, air pollution and contaminated food and mercury exposure through fish consumption, air pollution and dental amalgams (ATSDR, 1999a,b, 1990).

Given this evidence, we used data from the National Health and Nutrition Examination Survey (NHANES) 1999–2002 to examine the association between various heavy metals and endometriosis and uterine myomas. Given the estrogenic properties of cadmium, we hypothesized that cadmium would be positively associated with an increased odds of endometriosis and uterine myomas, whereas lead and mercury would show either no associations or protective associations.

**Materials and Methods**

**Data source**

We used data from NHANES 1999–2002 to examine the association between heavy metal levels in blood and having a previous diagnosis of endometriosis or uterine myomas. NHANES is a cross-sectional national survey that assesses the health and nutrition of children and adults in the USA through questionnaires, physical examinations and laboratory tests. In 1999, the survey became a continuous, annual survey with ~5000 individuals interviewed per year. The study population is a stratified, multi-stage probability sample of the civilian, non-institutionalized US population. From 1999 to 2002, the study was over-sampled for low-income persons, adolescents, persons over 60 years of age, African Americans and Mexican Americans. NHANES includes both a household interview and mobile examination component (MEC). Detailed information regarding the NHANES survey can be found from the study website (http://www.cdc.gov/nchs/nhanes.htm).

**Study population**

Women participating in the MEC and who completed the reproductive health questionnaire were eligible for analyses (n = 6815) (Fig. 1). Questions regarding endometriosis and uterine myomas were restricted to those women 20–54 years of age, reducing the eligible population to 2818 women. Women who were currently peri- or post-menopausal (n = 718), or pregnant and/or breastfeeding (n = 581) were excluded from analyses as their current heavy metal levels may have been influenced by these circumstances and less representative of heavy metal levels at the time of diagnosis (Berkowitz et al., 1999; Hertz-Picciotto et al., 2000; Garrido et al., 2003; Akesson et al., 2002; Dorea, 2004). An additional 94 women where excluded from analyses as they were missing data on heavy metal levels. This resulted in further limiting the age range of eligible women to 20–49 years of age as mercury was not measured on women 50 years of age or older on the assumption they had completed their childbearing years.

Diagnosis of endometriosis and uterine myomas was based upon two questions: (i) ‘Has a doctor or other health professional ever told you that you had endometriosis? Endometriosis is a disease in which the tissue that forms the lining of the uterus/womb attaches to other places, such as the ovaries, fallopian tubes etc.’ and (ii) ‘Has a doctor or other health professional ever told you that you had uterine fibroids? Uterine fibroids are benign (non-cancerous) tumors growing in various locations on or within the uterus/womb’. Women reporting disease were further queried regarding their age at first diagnosis. Additional information on menarche, gravidity, parity and hormone use was obtained from the reproductive health questionnaire. Data on other factors of interest such as demographics, alcohol and smoking were obtained from their respective questionnaires.

Blood was drawn during the MEC for the purpose of measuring heavy metal levels, with lead and cadmium measured for all individuals 1 year of age or older and mercury measured for individuals 1–5 years of age and 15–49 years of age. Blood was collected in EDTA-anticoagulant vacutainers prescreened for background metal contamination. Analyses for lead and cadmium were done by graphite furnace atomic absorption spectroscopy and mercury by cold vapor atomic absorption spectrophotometry. The limits of detection were: lead, 0.3 μg/dl; cadmium, 0.3 μg/l and mercury 0.2 μg/l.

**Statistical analysis**

Appropriate sample weights were used for analyses taking into account the complex sampling design and non-response of the NHANES survey. Sampling errors were estimated using the Taylor series linearized method. Women eligible and ineligible (pregnant, breastfeeding, peri- or post-menopausal or missing heavy metals data) for analyses, as well as eligible women with and without disease, were compared on various demographic, lifestyle and reproductive health factors using Pearson’s χ² test (categorical variables), Student’s t-test (continuous, normally distributed variables) and Kruskal–Wallis test (continuous, non-normally distributed variables). The association between tertiles of heavy metals and endometriosis or uterine myomas was assessed using unconditional logistic regression providing an odds ratio (OR) and 95% confidence interval (CI) for the association between exposure and disease. An OR greater than 1.0 indicates a greater odds of disease associated with exposure, whereas an OR less than 1.0 indicates a decreased odds of disease associated with exposure or a potential protective effect. If the CI does not include 1.0, then it is statistically significant. All three heavy metals were entered into the multivariable models together in order to examine the effect of the main metal of interest while controlling for the effects of the other two metals. Factors shown in the literature to be associated with heavy metals or the outcomes of interest or that changed the association between heavy metals and outcomes by more than 10% were examined as potential confounders. Furthermore in selecting potential confounders, we took into consideration the timing of diagnosis and measurement of exposure and whether current information on the confounder would be relevant to the exposure–outcome relationship. In the case of smoking and birth control pills, we were able to determine use in relation to the timing of diagnosis; however, we were unable to do so for alcohol consumption or BMI based upon the data collected and therefore did not include them as potential confounders. Parity and gravidity also were not considered as potential confounders as timing of diagnosis in relation to specific pregnancies could not be determined. Further analyses limiting cases to those diagnosed within the last 10 years and those diagnosed after their last pregnancy were undertaken given concerns that heavy metal levels may have changed over time. Additionally, we examined the association between metals and outcomes among post-menopausal women, given the high proportion of women with disease who had hysterectomies and were therefore...
excluded from the main analysis. A $P$-value of $< 0.05$ was considered statistically significant for all analyses. Stata, version 9.0 was used for all analyses.

**Results**

Women who were 20–54 years of age and responded to the endometriosis and fibroid questions were excluded from analyses if they were pregnant, breastfeeding, peri- or post-menopausal or had missing data on heavy metals (Fig. 1). Among excluded women ($n = 1393$), 48% were premenopausal, 13% were peri-menopausal, 35% were post-menopausal and menopausal status could not be determined for 4%; 21% reported having had a hysterectomy (data not shown). Ineligible women were significantly more likely to have been diagnosed with endometriosis or uterine myomas than eligible women ($P < 0.001$) (Table I). This was most likely due to the fact that the mean age of ineligible women was nearly 5 years older than eligible women ($P < 0.001$) and both endometriosis and myomas tend to progress until menopause. Furthermore, women with endometriosis or myomas were approximately nine times more likely to have had a hysterectomy than women without disease ($P < 0.001$) and were therefore more likely to be excluded from analyses. Eligible women also differed significantly from ineligible women by race/ethnicity, poverty ratio, marital status, BMI, smoking, alcohol consumption, gravidity, parity and ever use of birth control pills (Table I). Ineligible women had significantly higher blood lead levels, but significantly lower total blood mercury levels than eligible women; there was no significant difference in blood cadmium levels between the two groups.

Among the 1425 eligible women, 61 (6%) reported a previous diagnosis of endometriosis and 114 (8%) reported a previous diagnosis of uterine myomas. The above included 16 (1%) women who reported having a prior diagnosis of both endometriosis and uterine myomas (Table I). The mean age

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**Figure 1:** Study population for the association between heavy metals, endometriosis and uterine myomas, National Health and Nutrition Examination Survey (NHANES) 1999–2002
of the study population was 33.7 years. The majority of the population was White, non-Hispanic (67%), had more than a high school diploma (61%) and was married (61%). Approximately 25% of the women were current smokers and 22% drank more than two alcoholic drinks per week at the time of

the survey. Twenty-six percent of women had never conceived and 32% were nulliparous.

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the survey. Twenty-six percent of women had never conceived and 32% were nulliparous.

Women with endometriosis were significantly more likely to be White, non-Hispanic than women without endometriosis, but the two groups did not differ significantly by age,
education, use of birth control pills prior to diagnosis or smoking status at diagnosis (Table II). The mean age at endometriosis diagnosis was 27.0 years. Women with uterine myomas were significantly older (39.2 versus 33.0 years of age; \(P < 0.01\)), and more likely to be Black, non-Hispanic (21% versus 11%; \(P < 0.01\)) compared with women without uterine myomas. The mean age of uterine fibroid diagnosis was 33.5 years.

Women with endometriosis [geometric mean (GM) 0.53 \(\mu g/l\); 95% CI 0.44–0.64] had significantly higher cadmium levels compared with women without endometriosis (GM 0.42 \(\mu g/l\); 95% CI 0.41–0.44) (Table III). Women with uterine myomas had significantly higher lead (GM 1.25 \(\mu g/dl\); 95% CI 1.12–1.39 versus GM 1.12 \(\mu g/dl\); 95% CI 1.08–1.15) and mercury (GM 1.28 \(\mu g/l\); 95% CI 1.03–1.59 versus GM 0.97 \(\mu g/l\); 95% CI 0.92–1.03) levels compared with women without uterine myomas. Women who had diagnoses of both uterine myomas and endometriosis did not have significantly different metal levels than women who had neither disease (data not shown).

There was a dose–response association between cadmium exposure and endometriosis in unadjusted analyses with a statistically significant association between the upper tertile of exposure and disease (tertile 2 versus 1: OR \(= 1.80, 95\% \text{ CI} 0.68–4.77\); tertile 3 versus 1: OR \(= 2.84, 95\% \text{ CI} 1.13–7.13\)) (Table IV). This association persisted and became stronger after adjusting for lead, mercury, race/ethnicity, smoking status at the time of diagnosis, use of birth control pills prior to diagnosis and age (tertile 2 versus 1: adjusted OR \(= 1.94, 95\% \text{ CI} 0.73–5.18\); tertile 3 versus 1: adjusted OR \(= 3.39, 95\% \text{ CI} 1.37–8.40\)). A potential, non-significant protective effect was observed between mercury and endometriosis in both unadjusted and adjusted analyses. No association was observed with lead. There was a borderline significant

### Table II. Study characteristics by disease status, premenopausal women aged 20–49 years, NHANES 1999–2002.

<table>
<thead>
<tr>
<th></th>
<th>Endometriosis analysis</th>
<th>Uterine myomas analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Women with endometriosis (n = 61)</td>
<td>Women without endometriosis (n = 1362)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>85.4 (66.0)</td>
<td>66.0 (60.0)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>6.5 (12.4)</td>
<td>12.4 (14.1)</td>
</tr>
<tr>
<td>Hispanic/other</td>
<td>8.1 (21.7)</td>
<td>21.7 (24.3)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than HS diploma</td>
<td>9.7 (16.2)</td>
<td>16.0 (16.2)</td>
</tr>
<tr>
<td>HS diploma</td>
<td>27.3 (23.1)</td>
<td>23.1 (24.3)</td>
</tr>
<tr>
<td>More than HS diploma</td>
<td>63.0 (60.7)</td>
<td>60.7 (60.5)</td>
</tr>
<tr>
<td>Smoking status at diagnosis</td>
<td></td>
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<tr>
<td>Never</td>
<td>59.0 (60.6)</td>
<td>60.6 (60.6)</td>
</tr>
<tr>
<td>Former</td>
<td>6.3 (15.4)</td>
<td>15.4 (15.4)</td>
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<tr>
<td>Current</td>
<td>34.8 (24.0)</td>
<td>24.0 (24.0)</td>
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<tr>
<td>BC use prior to diagnosis</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>75.2 (75.7)</td>
<td>75.7 (75.7)</td>
</tr>
<tr>
<td>No</td>
<td>24.8 (24.3)</td>
<td>24.3 (24.3)</td>
</tr>
<tr>
<td>Mean age (95% CI)</td>
<td>35.2 (33.6–36.8)</td>
<td>33.4 (33.0–33.9)</td>
</tr>
<tr>
<td>Mean age at diagnosis (95% CI)</td>
<td>27.0 (25.3–28.7)</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Table III. Geometric mean (95% CI) heavy metal levels measured in whole blood by disease status (unweighted), premenopausal women aged 20–49 years, NHANES 1999–2002

<table>
<thead>
<tr>
<th></th>
<th>Endometriosis analysis</th>
<th>Uterine fibroid analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women with endometriosis (n = 61)</td>
<td>Women without endometriosis (n = 1362)</td>
</tr>
<tr>
<td>Lead ((\mu g/dl))</td>
<td>1.21 (1.04–1.41)</td>
<td>1.12 (1.09–1.16)</td>
</tr>
<tr>
<td>Cadmium ((\mu g/l))</td>
<td>0.53 (0.44–0.64)</td>
<td>0.42 (0.41–0.44)</td>
</tr>
<tr>
<td>Mercury ((\mu g/l))</td>
<td>0.87 (0.69–1.11)</td>
<td>1.00 (0.95–1.06)</td>
</tr>
</tbody>
</table>

*a*Lead levels were significantly higher among women with uterine myomas than women without uterine myomas (P-value Kruskal–Wallis test = 0.04).

*b*Cadmium levels were significantly higher among women with endometriosis than women without endometriosis (P-value Kruskal–Wallis test = 0.02).

*c*Mercury levels were significantly higher among women with uterine myomas than women without uterine myomas (P-value Kruskal–Wallis test = 0.01).
association between increasing mercury levels and uterine myomas in unadjusted analyses (tertile 3 versus 1: adjusted OR 1.86; 95% CI 1.02–3.39); however, this association was no longer significant after adjusting for lead, cadmium, race/ethnicity, smoking status at the time of diagnosis, use of birth control pills prior to diagnosis and age. We examined blood metal levels in relation to the number of years since diagnosis, as levels may have changed over time (Table VI). Only blood mercury levels were found to have changed significantly with years since diagnosis. When women diagnosed 10 or more years prior to participation in NHANES were excluded from analyses (25 women with endometriosis and 30 women with uterine myomas), the results did not change greatly overall; however, the association between cadmium and endometriosis became stronger (tertile 3 versus 1: adjusted OR 0.75; 95% CI 0.4–1.53) as did the association between lead and uterine myomas (tertile 2 versus 1: adjusted OR 0.83; 95% CI 0.39–1.77 and tertile 3 versus 1: adjusted OR 0.63; 95% CI 0.28–1.42) (data not shown).

In additional sub-analyses, we limited cases to only those that were diagnosed after their last reported pregnancy as pregnancies and breastfeeding have been shown to alter blood lead levels (Hertz-Picciotto et al., 2000; Dorea, 2004). This resulted in 36 women with endometriosis and 79 women with uterine myomas. Although the CIs became wider due to the smaller sample size, there was little change in the effect estimates in adjusted analyses. We also examined the association between exposure and disease among post-menopausal women given concerns of the large percentage of women with disease that were excluded due to hysterectomies. As the years since diagnosis was significantly greater in this population than the main study population (7.6 years since endometriosis diagnosis among premenopausal women versus 13.6 years since endometriosis diagnosis among postmenopausal women; \( P < 0.001 \)) and would therefore potentially influence heavy metal levels, we limited the analysis to only women diagnosed within the past 10 years. Although the analysis was limited by a small sample size \( (n = 26 \text{ women with endometriosis and 176 women without endometriosis}) \), the association between cadmium and endometriosis persisted, though not significant (tertile 2 versus 1: adjusted OR 0.71; 95% CI 0.31–1.63 and tertile 3 versus 1: adjusted OR 0.63; 95% CI 0.28–1.42).
diagnosis, use of birth control pills prior to diagnosis and age. These results are consistent with animal and human studies that have shown cadmium to be potentially estrogenic (Young et al., 1977; Stoica et al., 2000; Johnson et al., 2003; Brama et al., 2007). Blood mercury levels showed a potential protective effect in relation to endometriosis in adjusted analyses, consistent with the proposed anti-estrogenic effect of mercury (Young et al., 1977; Martin et al., 2003). After adjusting for potential confounders, no association was observed between heavy metals and uterine myomas, except a potential non-significant protective effect of lead.

The major sources of cadmium are through cigarette smoke (both active and passive), shellfish and green leafy vegetables with levels in food directly associated with contaminated water and soil. Among women with endometriosis, 35% were current smokers at the time of diagnosis, 6% former and 59% never smokers. This differed from women without endometriosis of whom 24% were current smokers at the time of the survey, 15% former and 61% never smokers. Cadmium tends to bioaccumulate in the tissues of the kidney and liver, but has been found in uterine tissue (Nasiadek et al., 2005) and follicular fluid (Zenzes et al., 1995) with levels significantly higher in smokers than in non-smokers (Zenzes et al., 1995). The half-life of cadmium in the kidney has been estimated to be 6–38 years (ATSDR, 1999a). Overall, our study population had low blood cadmium levels with 25% of women having levels below the limit of detection (0.3 μg/l) and 90% of women had levels less than or equal to 1 μg/l. This lack of variability in exposure limited our ability to detect significant associations; however, we still observed a statistically significant association between the upper tertile of cadmium exposure (≥0.5 μg/l) and endometriosis. Although cigarette smoke is associated with anti-estrogenic effects (Baron et al., 1990), cadmium, a contaminant in cigarettes, has been associated with estrogenic effects. Studies have shown that cadmium mimics estrogen activity in breast cancer cells and can bind to and inhibit the ERα receptor (Garcia-Morales et al., 1994; Young et al., 1977; Stoica et al., 2000; Brama et al., 2007). In rats, cadmium has been associated with earlier onset of vaginal opening, increased uterine weights and enhanced mammary development (Johnson et al., 2003), and decreased gonadotrophin binding and altered steroidogenic enzyme activity in granulosa cells (Priya et al., 2004; Nampoothiri and Gupta, 2006). In women, cadmium induced menstrual cycle abnormalities (Wang and Tian, 2004), difficulties conceiving (Wang and Tian, 2004) as well as preterm deliveries (Laudanski et al., 1991; Fagher et al., 1993).

Two previous studies investigating the association between cadmium and endometriosis found no association (Heilier et al., 2004, 2006). Both studies measured cadmium and lead levels at the time of diagnosis of peritoneal endometriosis (ENDO) and/or deep endometriotic nodules (DEN) and compared them with controls. Blood cadmium levels were extremely low in one study with a GM of 0.10 μg/l for all three groups, substantially lower than our study population (Heilier et al., 2004). The second study observed blood cadmium levels (DEN = 0.4 μg/l; ENDO = 0.3 μg/l; controls = 0.4 μg/l) similar to those we observed in the NHANES analysis (Heilier et al., 2006). In this study, they did find a borderline significant protective effect in relation to blood lead levels when comparing DEN alone (P < 0.05) and all types of endometriosis to controls (P = 0.046). Blood lead levels were slightly higher in this study population (all cases = 1.7 μg/dl; controls 2.2 μg/dl), compared with the NHANES analysis. This protective effect of lead is consistent with its hypothesized anti-estrogenic effect, but in contrast to the NHANES analysis which found no association, as well as a study of rhesus monkeys that observed an increased risk of endometriosis associated with lead exposure (Krugner-Higby et al., 2003). Only one study has examined the association of cadmium and uterine myomas, finding that cadmium tissue levels were significantly lower in myoma tissue than in the normal myometrium (P < 0.05) (Nasiadek et al., 2005). No studies examining the association between either lead or mercury in relation to uterine myomas were found in the literature.

This analysis has several limitations. As endometriosis and uterine myomas were self-reported, and not confirmed through medical records, it is likely there may be some misclassification of outcomes. We do not know if reported cases were confirmed surgically; and therefore, some reported cases may not truly be cases; however, within the Nurses’ Health Study, investigators reviewed medical records of women self-reporting an endometriosis diagnosis and were able to confirm 88.6% of all self-reported cases (Missmer et al., 2004). Conversely, some women may have had undiagnosed endometriosis or uterine myomas as they were asymptomatic or had not sought medical attention. The overall prevalence of endometriosis in our sample of eligible women (5.5%) was lower than the prevalence expected among women of reproductive age due to our exclusion criteria; however, the overall prevalence of endometriosis in NHANES from 1999 to 2002 was 9.4%, similar to that observed in other studies (Wheeler, 1989). If the misclassification of disease status is non-differential by exposure status, we would expect our results to be biased toward the null; however, if the misclassification is differential, the direction of bias could be in either direction.

Exposure misclassification is also a concern as exposure was measured after the diagnosis of disease, in some cases many years later. All three metals bioaccumulate in the body, which may result in an increase in blood metal levels since the time of diagnosis. However, in some instances, metal levels may decrease as has been shown with lead due to the mobilization of lead from bone during pregnancy and breastfeeding resulting in potentially lower levels in women who had intervening pregnancies (Hertz-Picciotto et al., 2000; Akesson et al., 2002; Garrido et al., 2003; Dorea, 2004). If heavy metal levels changed over time and are not representative of exposure prior to disease, it may bias the results. Taking this into consideration, we examined heavy metal levels by years since diagnosis, and did not see major changes in metal levels. We carried out sub-analyses excluding those women diagnosed 10 or more years prior to NHANES in one analysis and women diagnosed prior to their last pregnancy.
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in a second analysis and did not observe substantial changes in the risk estimates.

We excluded women who were peri- or post-menopausal, pregnant or breastfeeding due to concerns that their heavy metal levels would not be representative of levels at the time of diagnosis based on prior research (Berkowitz et al., 1999; Hertz-Picciotto et al., 2000; Akesson et al., 2002; Garrido et al., 2003; Dorea, 2004). This resulted in women who reported hysterectomies automatically being excluded from analyses. Overall, women in NHANES who reported a diagnosis of endometriosis or uterine myomas were approximately nine times more likely to report having a hysterectomy. By excluding these women, we limited our sample size and may have underestimated the true OR if there is an association between metals and disease, especially if these women represent more severe cases that would be more readily diagnosed. In further analyses, we did observe a positive, but non-significant association between cadmium and endometriosis among post-menopausal women when limiting analysis to women diagnosed in the past 10 years. No information was available regarding the staging of endometriosis, so we were unable to explore the effect disease severity may have on the association between exposure and disease.

Finally, given the limited research in this area, it is not clear what the critical window of exposure might be in relation to endometriosis or uterine myomas. In utero or early childhood exposures may alter the development of the HPO axis resulting in disease later in life; current exposures may target the HPO axis, resulting in altered gonadotrophin secretion; or alternatively current exposures may interfere with receptor binding or number leading to, or exacerbating, disease. The differences observed in the few studies examining the association between heavy metals and gynecological disorders may be related to the different timing of exposure assessment. These areas need further exploration.

The NHANES data provided a nationally representative sample in which to explore this research question making the study results generalizable to the USA. Consistent with other literature, White, non-Hispanic women were significantly more likely to have a diagnosis of endometriosis than other women; and Black, non-Hispanic women were significantly more likely to have a diagnosis of uterine myomas compared with other women (Marshall et al., 1997; Baird et al., 2003; Missmer and Cramer, 2003). In addition, both current and former smoking status at diagnosis showed a non-significant, protective effect for endometriosis and uterine myomas after adjusting for lead, cadmium, mercury, race/ethnicity, age and use of birth control pills prior to diagnosis, as has been reported elsewhere (Matorras et al., 1995; Baird et al., 2003; Louis et al., 2005; Tsukino et al., 2005).

These results must be interpreted with caution given the cross-sectional nature of this study with disease onset and diagnosis occurring prior to the measurement of heavy metals. Although the study lacks temporality of association, we have shown that lead and cadmium were not significantly different by time since diagnosis, especially among those with diagnosis less than 10 years prior to participation in NHANES. Despite the limitations of the NHANES data to examine this study question, we did observe a significant association between increasing levels of cadmium and endometriosis. This association deserves further investigation in a study designed to answer this question specifically.

References


